

### **REMARKS**

This is in response to the Office Action dated October 8, 2003. As requested by the Examiner, Claims 1 and 12 have been amended by changing the word "such" to --said-- in Claim 1 and changing "that includes" to --comprising-- in Claim 12. These changes are made without prejudice. In particular, applicants note for the record that neither change narrows their claims.

To simplify the prosecution of this application, applicants have canceled, without prejudice, composition Claims 29-38, and have amended Claim 1 by incorporating therein the limitations of dependent Claim 15 (now canceled). As a result of these amendments, all of the claims remaining in this application, i.e., method Claims 1-7, 9-10, 12-14, and 16-20, require topical administration of liposomes containing a ursolic acid compound (hereinafter referred to as "ursolic acid liposomes") so as to increase the ceramide content of the mammalian skin to which the ursolic acid liposomes are applied.

As discussed in applicants' specification, ceramides are critical to the barrier function of the skin (see, for example, page 13, lines 12-17, and page 23, lines 4-10, of the specification). Loss of barrier function, in turn, leads to increased transepidermal water loss and a sensation of dry skin (see applicants' specification at page 13, lines 29-31). It also makes the skin less able to protect the body from the effects of many agents including ultraviolet irradiation, toxic chemicals, toxins, and irritants (see applicants' specification at page 13, lines 14-17).

As illustrated in applicants' examples, in accordance with the invention, it has been found that the application of ursolic acid liposomes to skin cells (keratinocytes) results in increased ceramide content, both under in vitro and in vivo conditions (see Figures 5, 6, and 8). In particular, as

shown in Figure 5, in terms of total ceramide content, both liposomes alone and liposomes containing ursolic acid show such a ceramide increase, with the increase produced by the combination of liposomes and ursolic acid being greater than that produced by liposomes alone.

In the October 8<sup>th</sup> Office Action, the Examiner rejected applicants' claims as allegedly obvious over Granger et al., U.S. Patent No. 5,723,139 (Granger et al.), in view of Fontanel et al. FR 2 723 313 (Fontanel et al.) and Classen et al. CA123:208694 (Classen et al.). Applicants respectfully traverse this rejection.

Granger et al. summarize their work as follows:

A polycyclic triterpene carboxylic acid [e.g., ursolic acid] in combination with either retinol or retinyl ester resulted in a synergistic inhibition of keratinocyte differentiation. The effects of polycyclic triterpene carboxylic acids [e.g., ursolic acid] in combination with retinol or retinyl ester were analogous to the treatment with retinoic acid. (Granger et al., abstract; emphasis added.)

Treatments with retinoic acid, however, have just the opposite effect from that which applicants discovered for treatments with ursolic acid liposomes, i.e., rather than increasing ceramides, retinoic acid decreases them. Applicants discuss retinoic acid at page 6, lines 25-31, of their specification:

Retinoic acid is able to reverse the alterations of lipid synthesis that occur during differentiation, resulting in a 3-4-fold increase in phospholipids, a 3-fold decrease in sphingolipids (most notably, ceramides), a 9-fold decrease of acylceramides, a near 2-fold decrease of cholesterol and cholesterol sulfate, a 6-fold decrease of lanosterol, and a 3-fold decrease of FFA in living skin equivalents (Ponec and Weerheim, 1990, Meth. Enzymol. 190:30-41).... (emphasis added)

and again at page 8, lines 13-26:

Retinoic acid is well known as an agent for treatment of photoaged skin. Topical retinoic acid has been shown to restore collagen I levels that are reduced in photodamaged skin (Griffiths et al., 1993, New Engl. J. Med. 329:530-5). Restoration of collagen I levels correlate with a reduction of fine wrinkles in skin (Griffiths et al., 1993, New Engl. J. Med. 329:530-5). Although retinoids have been shown to alter lipids in cultured skin equivalents (Ponec and Weerheim, 1990, Meth. Enzymol. 190:30-41), there are no reports indicating that retinoids reverse aging or photodamage by altering lipid levels. In part, this may be because retinoids reduce ceramide levels in skin equivalents (Ponec and Weerheim, 1990, Meth. Enzymol. 190:30-41), and reduce the thickness of the stratum corneum when applied topically to human skin (Kligman and Leyden, 1993, Skin Pharmacol. 6, Suppl. 1:78-82), which could exacerbate the depletion of ceramides and barrier function that occurs in the aged. (emphasis added)

Thus, when Granger et al. describe their combination of a polycyclic triterpene carboxylic acid (e.g., ursolic acid) with a retinol or retinyl ester as being "analogous to the treatment with retinoic acid," they certainly cannot be disclosing or suggesting the present invention because retinoic acid decreases ceramide content, while the present invention, as set forth in amended Claim 1, increases ceramide content.

Moreover, Granger et al. repeatedly teach that polycyclic triterpene carboxylic acids are ineffective by themselves and need a retinol or retinyl ester to function in Granger et al.'s system. Thus, at column 1, lines 61-64, they write:

PTCA [polycyclic triterpene carboxylic acids, including ursolic acid] has no or little effect on improving skin benefit when used alone; a substantial increase in skin benefit is only realized when PTCA is combined with retinol or a retinyl ester.

Similarly, at column 9, lines 25-27 and 65-67, Granger et al. report that " $10^{-6}$  M glycyrrhizic acid [a ursolic acid compound] had no inhibitory effect on the keratinocyte TG1 level when used alone" and " $10^{-6}$  M oleanolic



acid [another ursolic acid compound] had only a very slight inhibitory effect on the keratinocyte TG1 level when used alone."

Applicants, on the other hand, found that ursolic acid compounds when administered in liposomes have significant effects on lipid production and, in particular, significant effects in terms of increased ceramide levels. Under these circumstances, applicants respectfully submit that the Examiner's primary reference teaches away, rather than towards, the present invention.

The Examiner's secondary references do not make up for the deficits in the primary reference. Nothing in Fontanel et al. suggests that ursolic acid compounds can be used to increase skin lipids in general or ceramides in particular. As to Classen et al., this reference is concerned with making liposomes in outer space and simply mentions that liposomes can contain phospholipids, but otherwise is unrelated to the present invention.

In summary, in view of the foregoing, applicants respectfully submit that the Examiner's rejection under 35 USC §103 should be withdrawn. Reconsideration and allowance of the application are thus respectfully requested.

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Respectfully submitted,

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